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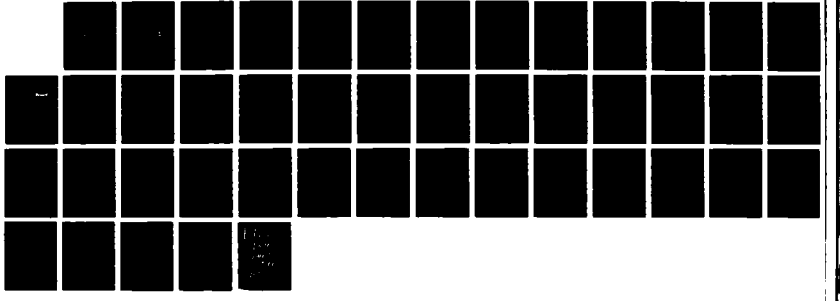

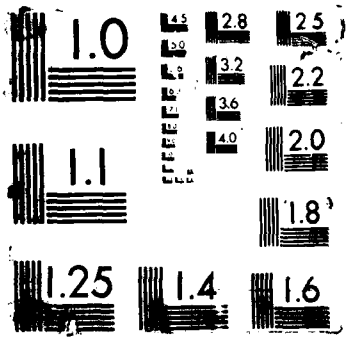
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FUNCTIONAL ASSESSMENT OF LASER IRRADIATION

ANNUAL REPORT

DAVID O. ROBBINS, Ph.D.

MARCH 1984 - FEBRUARY 1985

March 1988

Supported by

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Exposure of the retina to intense spots of coherent light produces immediate changes in the ability of the animal to perform a visual discrimination task. Relatively large shifts in visual acuity occur during laser irradiation and recovery is somewhat rapid following termination of relatively low-energy, long duration exposures. With more intense energies, recovery is slower and permanent shifts in postexposure spectral sensitivity often accompany these types of exposure conditions. Recommends:

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FOREWORD

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978.

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TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

INTRODUCTION

As the development and application of a wider variety of laser systems have increased, out of necessity so have studies of laser safety. A first step in establishing safety guidelines is determining the minimal energies necessary to produce ocular damage under a variety of different types of acute and chronic exposure conditions. This light form, both in its inherent properties and potential power levels, poses possible health hazards not common with other light sources. As a consequence users and others who might be exposed to laser light need to be protected from possible damage due to overabsorption. Damage to biological tissue can result from a brief, single exposure to a laser beam or from multiple exposures to power levels which initially produce no observable consequences.

Thresholds for ocular damage can be determined by traditional morphological means (fundoscopically or histologically) or can be defined in terms of changes in the visual sensitivity of the organism exposed as determined either behaviorally or through electrophysiological analyses of retinal function. In some ways the latter criteria may ultimately be the most important in determining the ability of an exposed soldier to successfully complete a visually-guided motor response. Furthermore, legal liability for treatment and provisions for medical disability will not be determined by the presence or absence of tissue alterations alone but by the presence of any perceived change in the ability of the person to perform visually.

Technological advances in other fields such as histology and electrophysiology have greatly improved the analytical methodology for assessing fine retinal damage as a result of light overstimulation. Associated with these methodological changes has been the demonstration that moderate as well as

intense light can produce permanent changes in retinal morphology (1, 2, 3). But predicted and observed damage thresholds became inconsistent, in part due to different assessment techniques with varying sensitivities for defining damage thresholds. Additional inconsistencies were the result of growing diversities within the delivery systems and wavelengths of new laser devices. For example, histopathological examination reveals retinal damage at lower exposure levels than are observed by ophthalmological examination alone especially when the area of retinal involvement is restricted. On the other hand, functional criteria are often considered to be the most sensitive, especially when considering wide field stimulation since subtle enzyme and photochemical changes as well as minute structural changes can cause shifts in visual sensitivity in cases where observable morphological disruptions are difficult or impossible to detect.

Even with functional criteria, however, thresholds for permanent shifts in visual sensitivity have varied depending upon the visual task used to assess function. Changes in the luminance, wavelength, and contrast of test targets have yielded various damage thresholds but most are considerably lower than those derived under maximum photopic conditions using achromatic targets and considerably below those derived using traditional morphological criteria. Relatively recent improvements in techniques for functional assessment (4) have even further lowered the functional threshold for acuity and provided the opportunity for the examination of the transitional zone between temporary and permanent shifts in visual acuity. This method eliminated the time delay for recovery from the anesthetic which was a part of all previous behavioral studies and which had prevented any postexposure testing for at least the first 24 hours. This restriction in previous behavioral methodologies also eliminated any possibility for the examination of changes in sensitivity during the early course of recovery and/or repair.

The present report utilizes this improved method for exposing awake, task-oriented rhesus monkeys and examines both the immediate and long term shifts in visual sensitivity following laser exposure.

There have been no direct systematic studies to examine any differential effect thermal and/or mechanical damage mechanisms may have on human visual sensitivity. Furthermore, due to the nature of laser safety investigations, the use of human subjects poses serious methodological and ethical problems that are not easily resolved. As a consequence, intentional human laser exposure has been limited to those eyes that suffer severe retinopathies or eyes which are slated for enucleation. The degradation of such eyes as well as the usual medical urgency for removal of the eye prevents the performance of complete postexposure testing on these subjects (5, 6). Therefore, for behavioral studies, a suitable animal model had to be found.

The selection of the rhesus monkey was based on the similarity of its retinal anatomy and physiology to that of the human and its comparable visual sensitivity. In spite of some small discrepancies, both the visual performance and retinal anatomy of the two species are remarkably similar, making the rhesus an excellent human prototype for these type of investigations. Furthermore, the position of this animal on the phlyogenetic scale and its implied superior intellectual abilities lead one to assume that the strategies employed by these animals to compensate for any lost visual function may not be significantly different from those employed by their human counterparts especially when considering the motivational level under which these subjects are tested.

As previously mentioned, functional studies are important in determining safety standards for laser irradiation since morphological criteria alone tell little about the degradation of visual performance accompanying any such damage. Furthermore, prior to the current effort, virtually no exploration of

exposures levels at or slightly below the transition from temporary to permanent visual losses has been conducted since no technique was available to expose an awake, task-oriented animal. Instead, early behavioral studies were restricted to the evaluation of severe retinal morphological disruptions of the rhesus fovea (7, 8, 9, 10). The effects of these foveal irradiation levels were usually permanent, producing impairment in visual acuity ranging from 40% to 80% of pre-exposure levels. In these previous studies, anesthesia was required for the placement of retinal lesions, thereby eliminating any possibility of immediate postexposure acuity measurements for at least 24 hrs. The inability of these former studies to measure transient changes in visual acuity at threshold and subthreshold energy levels, as well as a means to follow the initial phases of deficits elicited by suprathreshold energy levels, was a serious limitation. During the course of the current research effort, we have examined the immediate as well as the long term effects of single and repeated exposure to Argon (514 nm), HeNe (633 nm), and Krypton (647 nm) lasers. Various parameters of the exposure have been manipulated including energy density, duration, spot size, and position on the retina. Likewise, in an attempt to assess vision under a variety of photopic and scotopic viewing conditions, we have varied the background luminance, wavelength, and contrast of acuity targets of varying sizes and orientations. Although much work has been done in this area, there is still much to be determined not only to protect human observers from accidental exposure but also to prevent underutilization of lasers because of unrealistic restrictions placed upon its employment. In addition, as new laser systems are produced, new standards have to be developed to account for any changes in output energies, wavelengths, and/or durations. Further, the long term consequences of repeated exposures are less delineated than are those that result from the single exposure condition.

METHODS

A detailed description of the methods used to expose, awake, task-oriented rhesus monkeys has been presented elsewhere (11) and will be only briefly described here. This method has reliably produced foveal exposures in conscious animals and has allowed for the measurement of shifts in acuity and in contrast and chromatic sensitivity prior to and immediately following exposure.

SUBJECTS Male rhesus monkeys ages 2 through 8 and weighing 8 to 10 lbs. were used as experimental subjects. All animals were examined fundoscopically prior to exposure and, together with pre-exposure measurements of visual acuity, revealed no refractory errors or morphological abnormalities in their retinae.

All subjects were housed individually in standard primate cages and were free to move about in their home environment. Animals were fitted with a custom, light-weight, plastic neck collar for capturing purposes. The home environment was enriched with a variety of activities including TV, radio and play activities during the daylight hours. Light/dark cycles as well as temperature and humidity was controlled. The animals' diets and liquid intake were monitored and animals were under veterinarian supervision when housed in the laboratory. Each animal was routinely TB tested.

Apparatus. A restraint device was used during acuity testing to assure the animal's correct line of fixation and distance from the viewing screen. Restraint during exposure was necessary for proper placement of exposures on the central fovea since the animals were not anesthetized during this experiment. Historically, when the experimental paradigm requires temporary

restraint of the animal on a daily basis, chronic restraint devices such as primate chairs have been employed. Since the restraint period for this experiment extended over a period of months, such a procedure was judged to be detrimental to both the welfare of the animal and the purpose of the experiment. On the other hand, daily administration of anesthesia was judged to be detrimental to the general health and so a behavioral technique was developed for transferring animals from their home cage to the experimental cubicle. Often the animal in this situation is uncooperative either because of fear or adverse conditioning.

In our procedure, the animals were conditioned to enter a specially designed squeeze device which easily converted to a temporary restraint-type chair. Prior to training the animals were custom fitted with a 15 x 15 cm Plexiglas collar. Ketamine was used to temporarily immobilize the animal during fitting. Our animals completely adapted to wearing these collars within several hours following recovery from the anesthetic and we observed no health problems or chafing in animals chronically wearing these collars over a period of several years.

A description and diagram of the restraint device is shown in Figure 1. The entire restraint device was mounted on a hydraulic lift platform attached to a mobile cart. This portable cart allowed easy positioning of the device against the home cage when transferring the animal in or out of the device and in the experimental chamber when used for acuity testing.

All laser exposures and pre- and postexposure assessments of visual acuity were made in the same light-tight, sound attenuated chamber. A white noise generator was used to mask sounds generated by the experimental equipment located in a nearby room. The chamber measured 70" x 26" and contained mounting brackets to lock the portable restraint device in position once proper alignment with the viewing screen was assured. Mounted on the far

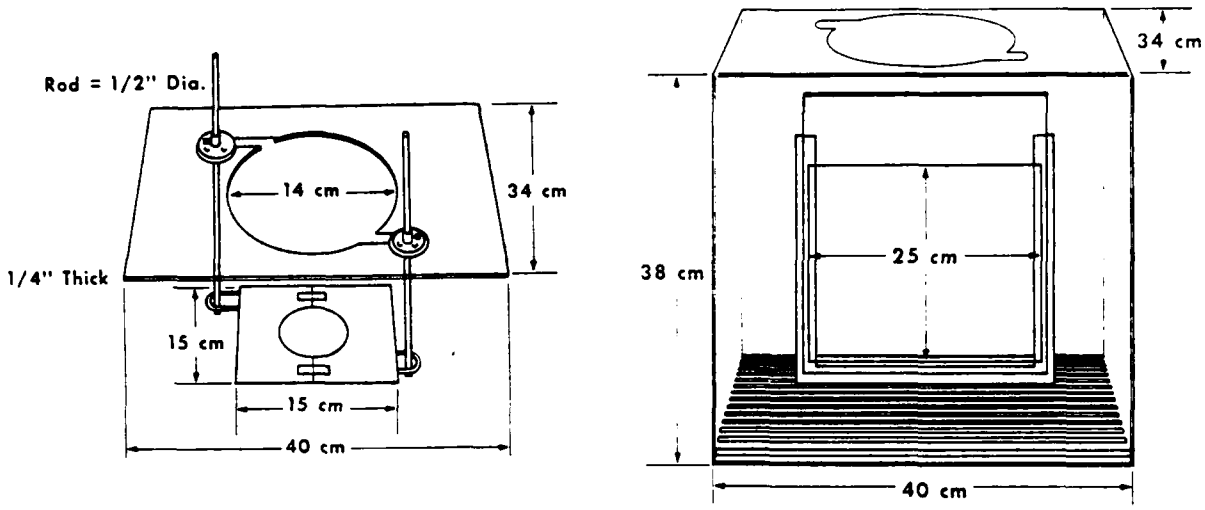


Figure 1. Diagram of the Plexiglas restraint device used during laser exposure and acuity testing. The overall dimensions of the cage, 40 w x 38 h x 34 d cm, readily accommodate rhesus monkeys of various sizes. The box was constructed of 3/8" Plexiglas with 1/2" aluminum rods forming the floor. Diagram of the collar, worn by the rhesus monkey, against the top panel of the restraint cage is shown in the diagram to the left. The poles are then secured with lattice frame base plates (hooks on the pole are not shown). The diagram on the right shows the Plexiglas door which when abutted against the door of the home cage, allows the animal to enter or exist. The top of the device contained a 14 cm diameter hole through which the animal's head could be projected. On either side of this hole, slots were cut through which rods with hooks could be inserted and attached to the rings on the animal's collar. These rods were used to draw the animal's collar up against the top of the restraint cage and assure fixation of the animal's neck. The animal was then custom fitted with a Plexiglas helmet which minimized head movements. An opaque facemask with adjustable iris diaphragms was aligned with the animal's pupils and, once inside the test chamber, positioned with the viewing screen so eye position could be tightly controlled. Small, voluntary head or eye movements by the animal would block the animal's line of sight with the viewing screen and could result in the animal being negatively reinforced for incorrect detections. As a consequence, subjects learned rather quickly to remain fixed in position once aligned with the screen. During the setup procedures, the animals were also positively reinforced with either fruit or juice for cooperative behavior and the animals were always physically separated from the experimenter preventing accidental injury to either party (12).

wall was a rear projection screen subtending 3 deg at a distance of 1 m from the animal's pupil. Two carousel projectors, positioned outside the

experimental chamber, served as the source for image projection and the background of the viewing screen. Luminances and wavelengths of both the viewing background and test targets were determined independently by neutral density and interference filters placed in the light paths. Both the image and background carousel projectors were programmable and were internally able to read a variety of coded slides.

Acuity was measured using standard Landolt rings and square-wave gratings. These slides were photographically produced on Kodak high contrast film (Kodalith) and were photographically reduced to produce different size targets. The Landolt rings were black on a clear background. The thickness of the Landolt rings and the width of the gap that formed the critical detail were always 1/5 of the diameter of the ring. The size of the gap could be varied from 0.25 to 30 min of visual angle in equal steps. The position and orientation of the gap in the Landolt rings was always in the same location on the screen. Except for the screen, the test chamber was entirely dark.

The presentation of slides, recording of the animal's responses, and consequences for the behavior were under the control of a LVE/BRS Interac System and Data General Nova 3 microprocessor. An Apple IIe microprocessor was also used for on-line data analysis, display, and storage.

Discrimination Task. Animals were trained using an avoidance paradigm to press a lever in the presence of a Landolt "C" and not to respond in the presence of a gapless Landolt ring. Failure of the animal to press the lever in the presence of a Landolt "C" (defined as "miss") or lever pressing in the presence of gapless rings (defined as a "false positive") resulted in the presentation of a discriminative tone and, on a variable reinforcement schedule, a brief, weak electrical shock. The shock was obtained from the secondary of a high-tension coil by discharging a capacitor into the primary, and was annoying but not highly painful as the authors can testify from

experience. Swinnen, Brady & Powell (13) have concluded that because of its short duration this type of shock is safer for rhesus than conventional electric shock. . The use of negative reinforcement during testing was necessary in order to consistently maintain the animal's vigilance during the course of testing and especially immediately following laser exposure. A well trained and vigilant animal could avoid shock altogether.

Following shaping, threshold acuity testing was derived using a modification of the von Bekesy tracking technique (14). In this technique, if the subject correctly detected the Landolt ring by pressing a lever (hit), a discriminable tone was presented and the next series of Landolt rings and gapless rings was 20% smaller. Incorrect detection of the Landolt ring (miss) resulted in a different discriminable tone, the possibility of a brief shock on either a fixed or variable ratio schedule, and the presentation of rings 20% larger. To discourage the animal from responding indiscriminately to all rings, a third discriminable tone was presented immediately following lever responses to gapless rings (false positive) and, on a fixed ratio schedule, the animal received a brief shock for these incorrect responses. The number of false positive responses was always low in trained animals (less than 10%). Using this paradigm, the size of the threshold target was always at the animal's threshold thereby eliminating time spent testing targets either significantly above or below threshold. The test objects were typically presented in sets of four rings that were of equal diameter. Three of the rings in each set were gapless, while the fourth was a Landolt "C" that appeared in a random position within the set. Each ring was projected for 2 sec. and there was a 1 sec. dark interval between successive rings. The size of the test series was shifted only on responses to Landolt "C" rings and not to gapless rings. Baseline means, variability, and false positive responses in both the exposed and control eye were monitored daily throughout the

experiment.

To measure threshold acuity under a variety of viewing conditions, the background upon which the darkened test target was projected could be varied by a second projector in terms of its luminance, wavelength and contrast. All

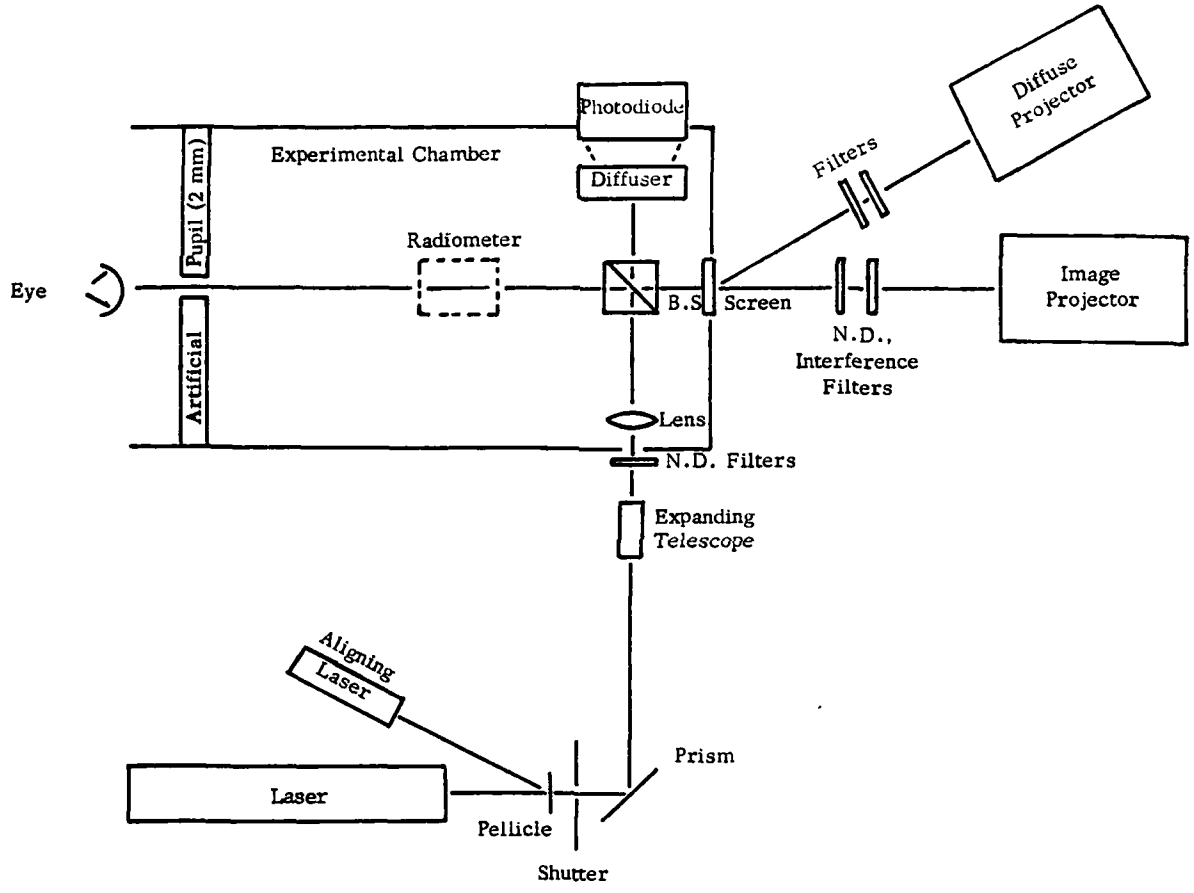


Figure 2. Diagram of the laser and image optical system. Various laser systems have been used as exposure sources including HeNe (632.8 nm), Krypton (647 nm) Argon (514.5 nm), and Nd/YAG (514.5). The position and the size of the beam on the retina was controlled by the expanding telescope and the converging lens used to present the spot in Maxwellian view. An electronic shutter controlled exposure duration for CW lasers. Discriminable stimuli were presented by a programmable Kodak carousel projector while a second programmable projector was used to vary the contrast of the darkened target against a light background. The animal within a restraint apparatus was positioned behind a wall such that it could monocularly view the screen and discriminanda only by looking through a small fixed, artificial pupil.

measurements were made under monocular conditions and after the animal had adapted to the luminance level of the screen.

Laser System. A 4.0 W CW Argon laser (Spectra Physics, Model 165/265) served as the laser source. A small HeNe laser was used for aligning purposes. A diagram of the optical system is shown in Figure 2. The entire laser system, with the exception of a beam splitter and focusing lens, was mounted outside the experimental chamber. The "raw" laser beam passed first through several neutral density filters for attenuation and then through a manual safety shutter. The attenuated beam was then directed through an electronic shutter which produced a calibrated exposure of between 1 and 100 msec when triggered electronically by the experimenter. The beam was then diverted by a 4.5 cm diameter front surface mirror and entered a beam expanding telescope which produced a collimated beam of adjustable diameter between 100 and 500 microns. When a minimal diameter spot (<50 microns) on the retina was presented, the expanding telescope was removed from the optical system. The expanded beam was then directed through a final focusing lens and a 5 x 10 cm coated pellicle beam splitter placed at the intersection of the diverging laser beam and the beam from the rear-projection viewing screen. The converging beam then passed through a final 4 mm aperture positioned just in front of the animal's natural pupil.

Mounted on the opposite side of the beam splitter was a diffuser and ultrafast photodiode (HPA 4203). The output of this detector was displayed on a memory oscilloscope and was regularly calibrated against an EFF Model 580 Radiometer placed at the corneal plane. The power and pulse width of each laser exposure was measured and recorded.

Proper alignment of the laser beam with the animal's pupil was critical. The laser beam was presented to the animal coaxial with a line between the artificial pupil and the gap in a specified, threshold Landolt ring which

subtended less than 1 minute of arc. For determinations of the line of sight, a 2 mm aperture was placed on the screen over the position of the gap in the specified Landolt ring. A mirror, approximately 2 m behind the 4 mm artificial pupil was then adjusted until it was normal to the line of sight. With the converging lens removed, the beam splitter at the junction of the image and laser beams was then aligned so that the collimated beam from the laser passed through the 4 mm aperture and was reflected off the mirror back onto itself and through the 2 mm aperture at the projection screen. Coaxial alignments with the line-of-sight were then verified by noting that the reflected beam passed through both apertures and back on itself without any loss. The focusing lens was then positioned such that the cornea was in the focal plane of the lens and so as not to change the alignment of the beam with the light-of-sight adjustment. Presenting the beam in Maxwellian view reduced the possibility that changes in pupil diameter or small lateral movements of the animal's head would affect the amount of light entering the eye.

This laser system was capable of presenting single-pulsed exposures ranging from less than 100 msec to greater than 10 min. In those instances where acute exposures were made, exposure durations of less than 100 msec were used to avoid the confounding effect of involuntary and voluntary eye movements away from the spot. Such movements would spread the irradiation over a larger retinal area than that produced by the optics of the laser system and the eye itself. Corneal power densities of greater than 2 W over a retinal area of from less than 50 microns to greater than 500 microns in diameter was possible. Within limits, the location of the exposure on the retina (on- or off-axis) could be varied by adjusting the position of the beam relative to the animal's point of fixation on the viewing screen.

Laser exposure. Prior to any laser exposure, stable acuity levels were established for each of the subjects' eyes. A criterion of, at minimum, 14

consecutive sessions of threshold measurements was used to establish a mean and standard deviation acuity level for a number of different viewing conditions. Acuity was derived using a variety of monochromatic and achromatic backgrounds under different luminance and contrast conditions.

Prior to each exposure, pre-exposure acuity was derived for each eye during a 15 - 20 min test session. Failure of the animal to obtain a mean acuity within one standard deviation of his predetermined acuity level aborted the laser exposure. Session variability or increased false positive responding beyond a pre-established level also aborted the session. In cases where the animal did not achieve his pre-exposure baseline level in an eye which had previously been exposed, testing was continued to establish the parameters of the visual deficit.

All exposures were made while the subject was actively discriminating threshold Landolt rings. Postexposure testing began immediately after each exposure and continued until the animal was able to re-establish his baseline level or until the session was terminated due to time. The laser flash was triggered immediately after the animal correctly detected a specified threshold Landolt. In previous studies using closed circuit television, it has been observed that our animals maintain fixation on the critical feature of the target for seconds following responding and until reinforced either with the discriminable tone or shock. No exposures were made following incorrect detections of threshold targets or following correct detections during the final 1 sec of the trial. Using this procedure immediate and significant downward shifts in acuity were noted in over 75% of the exposures presented. In those cases where no such downward shifts in acuity were noted, it is possible that involuntary or pre-established voluntary eye movements may have lead to exposures in the peripheral regions of the retina. Given the nature of our acuity task, exposure of this region of the retina would not

have been difficult to detect. Control or sham exposures with the laser beam blocked at the point of the safety shutter tested for any factors within the procedure which might change the animal's expectancy and response criterion.

Typically, only one exposure was made per session and in cases where the animal failed to return to his pre-exposure level during the exposure session, no exposures were made in subsequent sessions until a new baseline acuity level was established. At each power density, a repeated design was employed for each of the different types of viewing conditions employed. The order of viewing conditions under which exposures were made was random while the order of laser power densities presented was fixed, beginning first with the lowest and increasing in a stepwise order following completion of all viewing conditions. Postexposure testing was terminated after the animal had regained his pre-exposure acuity level for the given viewing condition or after 2 hrs of testing whichever came first. The animal's unexposed eye served as a control.

Statistical analyses of the data. Descriptive analyses of shifts in acuity were made for each exposure under each viewing condition. Since the number of exposed animals was relatively small, between subject analyses was limited and the majority of the analyses were made within subjects. Statistical comparisons were made of the changes in the degree and duration of the initial deficit as well as the total time for full recovery as a function of different exposure energies, durations, spot sizes, and wavelengths. Also examined was the effect the specific acuity task had on the magnitude and duration of the visual deficits. For each exposure paradigm, several different background conditions were examined under both photopic and scotopic viewing conditions.

The determination of the animal's performance level using the tracking technique was derived using the formula developed for the "Up and Down"

procedure (15). The traditional means of presenting the data was to graph the average acuity maintained within each running two minutes following exposure. This data could be graphed either in terms of the "Up and Down" procedure (raw data) or in terms of average visual acuity.

RESULTS

Complete baseline sensitivities were measured for each animal and for each eye prior to any laser exposure and were measured routinely throughout the period while the animal was receiving laser exposures. These baseline sensitivities often served as the reference for any observed deficit elicited by laser irradiation. Continual comparisons were made pre- and postexposure within the exposed eye and between this eye and the control eye which never received laser irradiation.

The initial effect of a brief laser exposure focused on the fovea is to produce an immediate shift in visual sensitivity followed by a gradual recovery in sensitivity over time provided the energy of the flash is below the threshold level for a permanent shift in acuity. A typical example of this effect on the ability of the animal to maintain maximum resolution on a photopic visual task is shown in Figure 3. In this figure recovery from a brief, 100 msec flash of 632.8 nm light is shown. This figure represents the ability of one animal to track acuity immediately following exposure. Time, relative to exposure, is indicated on the abscissa. In the left-hand portion of the figure, acuity for a tracking task is shown for a 15 min period immediately preceding laser exposure. During this pre-exposure testing using a typical 4:1 ratio of gapless rings to Landolt C's, pre-exposure mean acuity was 1.25 (min of arc)$^{-1}$. Acuity was defined as the reciprocal of the visual angle subtended by the gap in a Landolt C at the 50% threshold point. Preceding the exposure, the S was transferred to a 2:1 ratio of gapless rings

to Landolt C's and tested for an additional 2 min. The shift from 4:1 to a 2:1 ratio of gapless rings to Landolt "C"s was used to more rapidly access shifts in acuity and did not affect either the animal's response criteria or false positive rate. In this session, the animal was exposed to a single 100 msec laser flash following the correct detection of a 1.16 (min of arc)$^{-1}$ Landolt C which corresponded to the zero point on the abscissa of this figure. Immediately after exposure, the animal's acuity decreased to 0.51 (min of

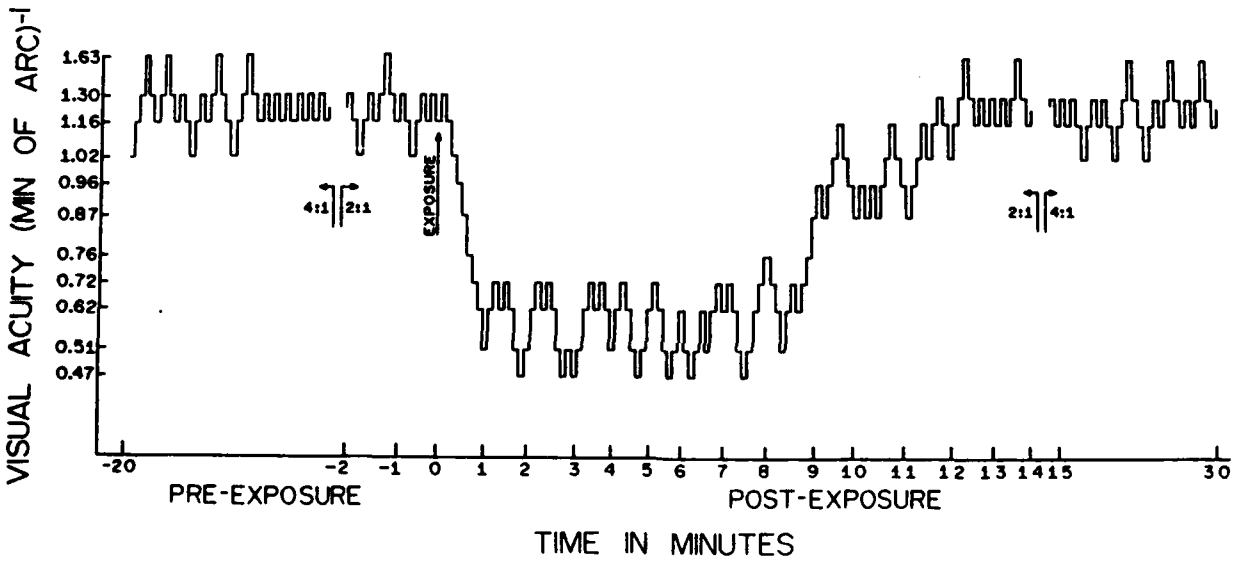


Figure 3. Sample raw data demonstrating the immediate drop in visual acuity immediately following laser irradiation. The occurrence of the 100 msec, 7mW, 632.8 nm exposure is indicated in the figure by an arrow, and corresponds to the zero point on the abscissa. The ordinate indicates the various sizes of the gaps in presented Landolt rings and is plotted in reciprocal visual minutes of arc. This scale is measured in discrete steps, since the vertical excursions of the plot were taken from a nonlinear potentiometer mounted on the slide tray of a carousel which recorded tray position. The abscissa represents the presentation of the Landolt Cs; corresponding times (in minutes) for representative trials are indicated relative to exposure.

arc)$^{-1}$, which corresponds to an acuity deficit of 59% relative to its pre-exposure acuity. This visual deficit lasted 9 min before the subject's acuity

gradually returned to its mean pre-exposure level. Total recovery from the initial deficit was complete in approximately 13 min. Threshold testing using the 2:1 ratio of gapless rings to Landolt Cs was continued for 3 additional minutes. The ratio of gapless rings to Landolt Cs was then shifted back to 4:1, and postexposure acuity measurements were extended for an additional 15 min. No permanent shift in pre- and postexposure acuity was found at the energy level (7 mW) used in this figure.

Using different laser systems including HeNe, Krypton, Argon, and Nd/YAG, we have explored the relationship between the magnitude and duration of any elicited deficits and the energy of the exposure. For descriptive purposes, the observed recovery process has been divided into two portions, an initial, rapid decline and eventual stabilization of acuity lasting anywhere from several minutes to hours followed by a gradual recovery to pre-exposure acuity levels for those energy densities where full recovery was observed. In those instances where recovery was not observed, typically the animal's postexposure acuity stabilized at the initial depressed acuity level often for several months before any further changes were noticed.

In previous studies we have noted that the magnitude of the initial deficit is related primarily to spot size rather than exposure energy, although exposure duration does affect the magnitude of the elicited acuity deficit. In this contract period we have continued to explore the relationship between spot size, exposure energy and duration on the magnitude of the initial deficit and the total time for full recovery. As previously reported, exposure energy was primarily related to recovery time while both spot size and exposure duration had more of an influence on the initial deficit.

Typically, immediately after exposure, acuity dropped to approximately 70% of its pre-exposure level and, depending upon the energy of the flash,

remained at this depressed level for several minutes before gradually returning to its pre-exposure baseline level. During the course of the deficit, the animal appeared vigilant and did not alter his detection criteria as seen in an unchanged false alarm rate. Sham exposures in which the paradigm was identical but the laser flash was not delivered to the eye being tested yielded no change in visual performance or response criteria. An example of the type of deficit produced by an acute exposure is shown in Figure 4. The recovery time course observed here was significantly longer than that usually experienced for photopic bleaching but the energy level employed here was below that necessary to elicit a permanent functional alteration. In this figure the effects of two different power densities of Argon flashes (2.0 mW and 3.0 mW) are shown along with sham exposures where no laser flash was presented. In the sham condition, the size of the projected discriminanda was shifted to the animal's pre-established immediate postexposure acuity level and the animal's acuity was then followed until it returned to its pre-exposure baseline level. In our paradigm, it took approximately 2 min for the equipment to track back to the animal's previous acuity level. The vertical bars around the data points represent $\pm$ 1 SD about the animal's mean acuity and demonstrate very little variance in the animal's performance under these conditions. Each data point represents the average of 4 - 6 different sham exposures presented over several weeks of testing. When the animal was exposed to laser irradiation, his derived acuity did not recovery immediately but remained depressed before gradually returning to its pre-exposure level. In these instances, the variability across sessions was much larger indicating postexposure performances following laser irradiation were not as predictable as the animal's normal baseline acuity.

As in previous examples, recovery was most rapid (10 - 14 min) when the power densities were low but these recovery times were greater than

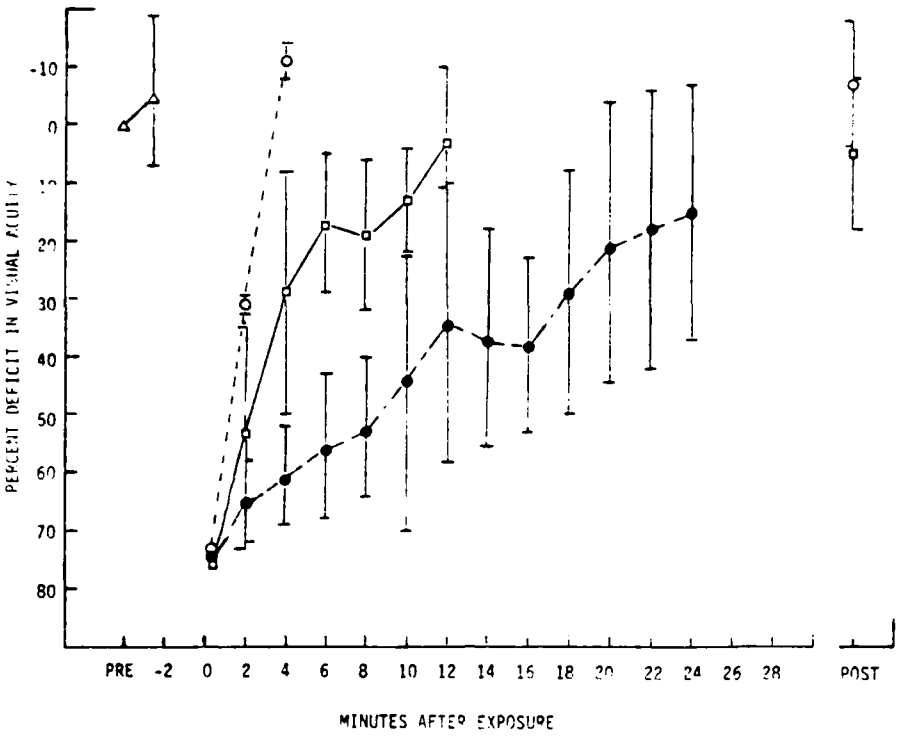


Figure 4. Recovery functions for one animal following 2.0 mW and 3.0 mW Argon (514.5 nm) flashes. Each data point represents the mean of 4 - 6 exposures. Only one exposure was made per day and a random design for power densities was employed. The open circles represent sham exposures where no laser flash was presented. The squares indicate recovery from 2.0 mW exposures and the dark circles recovery from 3.0 mW exposures. The vertical bars represent a variance of one standard deviation about the animal's mean acuity for that time period following exposure. Acuity was measured under maximum photopic conditions with a high contrast (97%) white light background.

expected for photopic recovery following full bleach of the foveal receptors. With more intense energy, recovery was delayed and in some cases was not complete within 30 min following exposure. In all cases under these exposure conditions, the subject had returned to pre-exposure acuity levels within 24 hr and no long-lasting, postexposure deficit was noted regardless of the type of viewing conditions presented.

The previous two figures focused on the transient effects that relatively low energy laser irradiation have on immediate postexposure visual acuity. In these cases, full recovery was typically complete within the 45 min

postexposure test session. When higher energy levels were employed, however, full recovery either was delayed for several days or impossible to achieve. In these cases, further exposures were postponed or suspended and complete analyses of postexposure sensitivity were made under a variety of viewing conditions. The laser energy level associated with a permanent functional change was defined as a threshold value for that particular viewing condition. As previously mentioned, this value varied across laser systems and was different depending upon the type of viewing condition used to assess postexposure functioning. There was also some variability across animals although these differences were relatively small and might be explained in terms of cumulative consequences of preceding exposures which were not necessarily the same across animals.

Generally, the animal's postexposure visual sensitivity following a permanent functional alteration was followed for a period of 6 to 12 months. During this time no further laser exposures were made and often there was some recovery especially in postexposure spectral sensitivity. In those animals that demonstrated a functional impairment that lasted longer than 96 hr, however, full recovery was rarely achieved across all postexposure assessment criteria. In these animals, postexposure testing continued for 12 to 18 months after the last exposure and the animal's sensitivity in the exposed eye compared to its previous pre-exposure level and the acuity in the unexposed, control eye. Long term testing in the exposed eye produced greater day to day variability than the animal had previously shown even though no such differences were found in the unexposed eye which was also tested during this same time period.

An example of the changes in postexposure spectral sensitivity is shown for one animal in Figure 5. Spectral sensitivity curves were derived from monochromatic intensity/luminance functions measured prior to and following

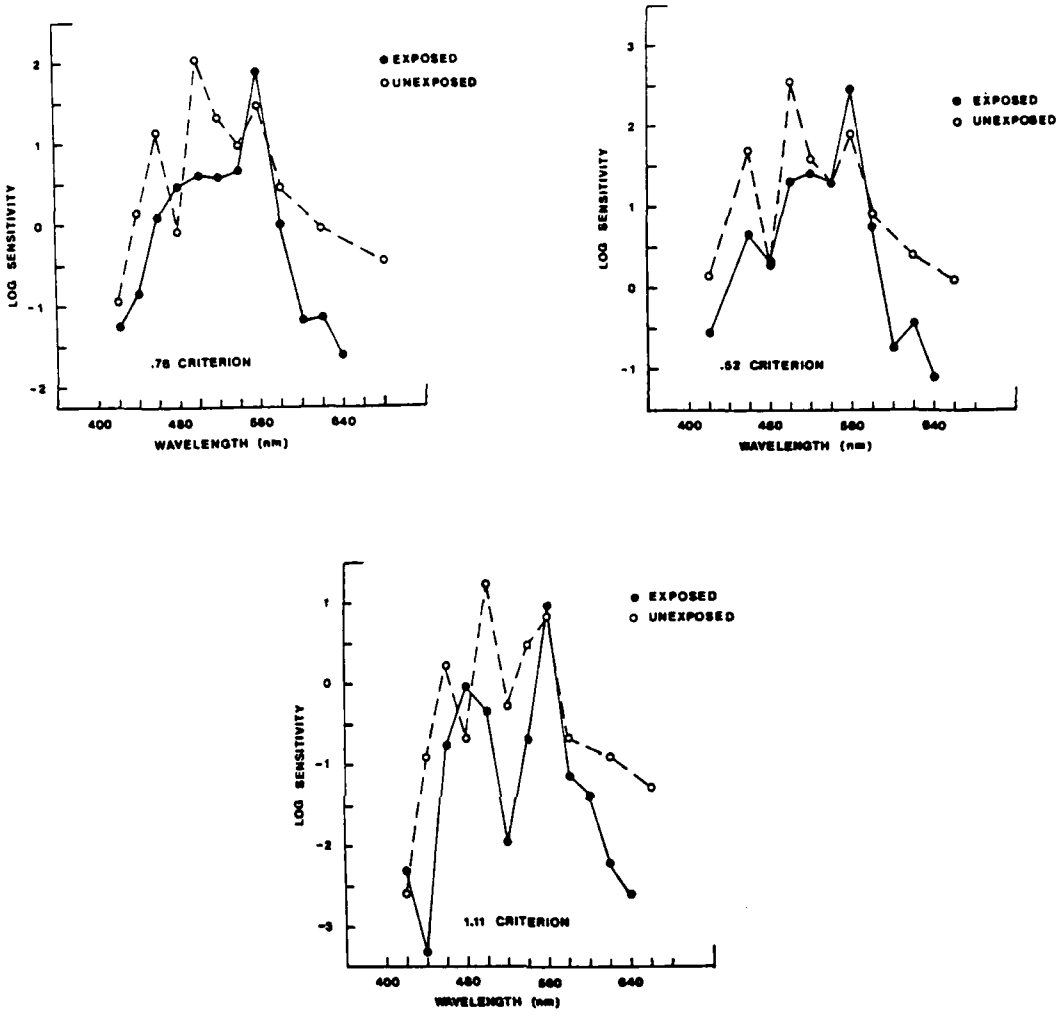


Figure 5. Comparison of pre- and postexposure spectral sensitivity in an animal exposed to a 100 msec, 3.0 mW Argon (514.5 nm) flash. Spectral sensitivity curves were derived from individual intensity/acuity functions determined at each of specific wavelengths shown. Each intensity/acuity function was the average of several days of postexposure testing at each of at least five different luminance levels over a 5.0 log unit range. Acuity levels ranged from 20/15 to 20/100 in Snellen terminology. Least squares lines were derived for each spectral background and the correlation coefficients ranged from 0.89 to 0.97. Spectral sensitivity curves at various criterion acuities were derived for these equations. A repeated measures, rapid design was employed during both the pre- and postexposure test session. The open circles represent pre-exposure sensitivity while the filled circles represent postexposure sensitivity. The criterion chosen are representative of maximum (photopic) and intermediate acuity levels.

exposure to an Argon (514.5 nm) flash which produced a permanent shift in chromatic visual acuity. The different curves represent different acuity criterion (0.52, 0.76, and 1.11). Pre-exposure peak sensitivity for this animal was 520 nm but shifted somewhat toward 560 nm when higher acuity criteria were employed. Sensitivity to both short (below 480 nm) and long wavelengths (beyond 560 nm) dropped off rapidly for all criteria employed. Postexposure spectral sensitivity for this animal was derived during the first month following the last laser exposure. Peak spectral sensitivity during this postexposure period shifted markedly to 560 nm for all criteria employed and postexposure acuity in this spectral region, adjusted for luminance, was slightly higher than the animal's pre-exposure level. The maximum shift between pre- and postexposure spectral sensitivity was found in the neighborhood of 500 to 520 nm which corresponded to the wavelength of the exposing source (514.5 nm). Significant decrements in postexposure spectral sensitivity were also found for long wavelengths (beyond 580 nm) and these decreases were greater than those observed for short wavelengths for all criteria shown.

In the previous figures we have shown what effects acute, brief exposures to laser irradiation have on visual performance immediately following the termination of the laser flash. The energy density of these exposures while significantly above that ordinarily associated with full bleach light exposures were below the ED_{50} for distinct morphological damage. These energy densities were intense enough to produce relatively long term or even permanent changes in visual functioning although fundoscopic examination of these animal's fovea revealed no distinct morphological damage. The exposure paradigm used in these studies was meant to simulate what consequences a single, brief (100 msec) laser flash might have on visual performance in a wide variety of viewing conditions. In the next series of figures we have

examined what effects relatively low energy, long duration exposures have on visual performance both during the presentation of the laser irradiation and immediately following its termination. These experiments simulate the degradation of visual performance during exposure to laser irradiation. The energy levels employed here were several log units below those necessary to elicit a permanent functional deficit and significantly below the ED_{50} level for gross morphological damage as calculated for our exposure conditions. This type of paradigm simulates what one might find when attempting to fixate on a target seen through a "cloud" of laser light. We have used the term "cloud" since the animal's involuntary and voluntary eye movements would spread the laser irradiation over a significant portion of the retina even during periods of fixation on a target superimposed on this field. We have referred to these studies as our glare experiments although clearly other mechanisms may also be operating to produce the observed decrements in visual performance besides that of contrast.

A typical example of the raw data collected in this phase of our project is shown in Figure 6. This figure shows the computer printout of our up-down procedure for tracking changes in visual acuity over time. Prior to exposure, the animal baseline acuity was derived using standard Landolt rings on low contrast, achromatic backgrounds. Pre-exposure acuity for this animal under these viewing conditions was approximately 0.833 $(\text{min of arc})^{-1}$ or 20/24 (in Snellen terminology). At the time marked "0" on the abscissa, a shutter blocking the output from an Argon laser was opened and the laser beam presented to the subject. The optical system for presentation of the laser beam was identical to that used previously and produced an exposure which could be varied in terms of its retinal diameter, position relative to the animal's fixation point (gap in the discriminanda), and energy. The duration of the exposure was controlled by an electronic shutter and typically was open

for periods of 10 minutes or longer while the animal was required to track his visual acuity.

As demonstrated in Figure 6, immediately following the presentation of the laser exposure (marked 'laser on'), acuity decreased to approximately 0.15 (min of arc)$^{-1}$ or a Snellen acuity of 20/130 in approximately 5 min. The acuity of this animal remained at this depressed level for the duration of the exposure (10 min) before gradually returning to the animal's original acuity level in approximately 10 min after the laser irradiation was terminated

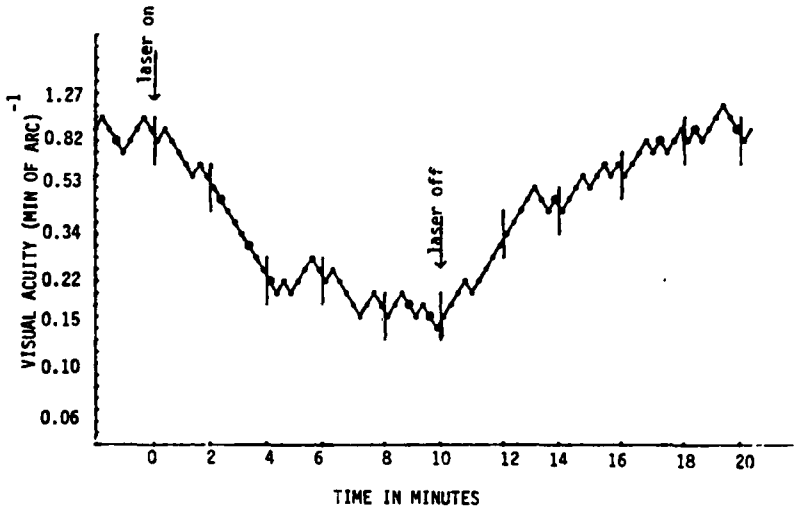


Figure 6. Changes in visual acuity during and immediately following the presentation of relatively low-intensity, long-duration, Argon laser irradiation - glare experiment. This animal was exposed to a 200 micron spot of 0.001 uW for approximately 10 minutes and during this time the animal's acuity was tracked using the up and down procedure. The same optical system as used previously delivered the laser beam in a line coaxial with the gap in the Landolt rings. Hence, the gap which the animal needed to detect in order to make the required discrimination was seen through a "cloud" of laser light. While the position of the beam on the retina might vary as the animal's eye moved, the discriminanda was also centered within it. The size of the beam was nearly double the size of the gap for maximum acuity targets when viewed on the screen. The vertical lines through the data represents a running two minute account of time. The data points themselves represent the presentation of Landolt "C"s and the vertical excursions the presentation of gapless rings.

(marked 'laser off'). The rate of recovery following the termination of the laser exposure was reminiscent of that seen for brief, 100 msec flashes. The maximum visual decrement elicited represented an acuity deficit of 82% from its pre-exposure baseline level and may represent the visual resolution of peripheral areas as more and more central areas became bleached with continued laser exposure. In this example no permanent shift in postexposure acuity was

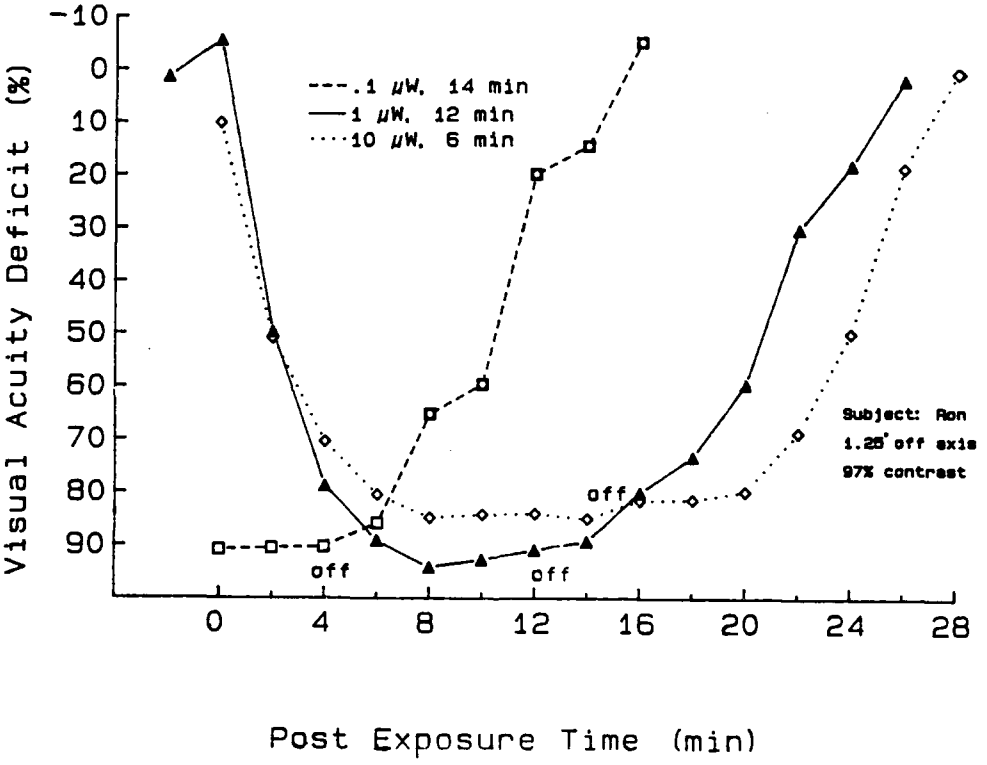
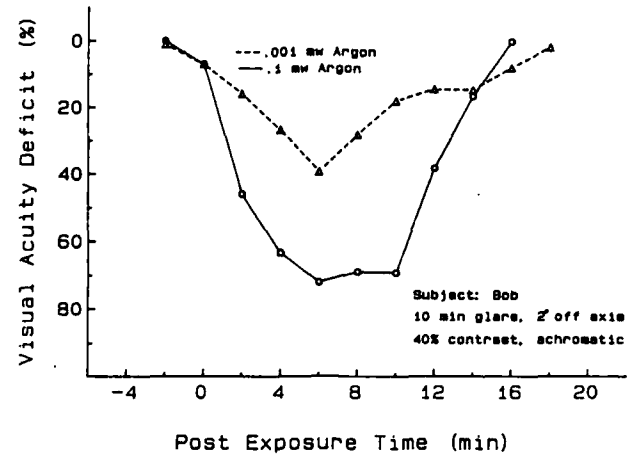


Figure 7. Shifts in baseline acuity during and immediately following low-intensity, Argon irradiation at three different power levels - glare effect. This animal was exposed to a 200 micron spot of 10.0, 1.0, or 0.1 uW. The 10.0 uW exposure was presented for 5 min; the 1.0 uW exposure for 13 min and the 0.1 uW exposure for 14 min. During this time the animal's acuity was tracked using the up and down procedure. The position of the beam relative to the break in the Landolt ring was 1.25^{o} from its center but still covered the animal's view of it. The termination points for each exposure is indicated by an arrow (marked "off") while its onset was at the "0" mark on the abscissa. The data points represent the mean of each running two minutes of acuity testing.

observed and 24 hr later the animal's visual functioning was entirely normal.

Figure 7 demonstrates a similar shift in visual acuity (plotted in terms of percentage deficit) during and immediately following exposure to laser "clouds" of varying energies. The three functions represent the visual deficits elicited by each of the three different exposure energies employed. When a relatively intense beam (10 uW) was presented, immediately visual performance dropped 90% to an acuity level almost below our ability to measure. This acuity level (20/140) represented activity of the more peripheral retina as the central areas became progressively bleached as the exposure continued. Not apparent was the continued drop in acuity to beyond our ability to track and hence the laser exposure was terminated approximately 4 minutes after its onset. Once the shutter was closed, the animal's acuity slowly returned to its pre-exposure baseline in approximately 10 min without evidence of any permanent consequence. When the "cloud" was made less intense (1 uW), the drop in acuity was slower but, at its maximum, was nearly identical to that seen with an exposure 10 times its energy level and almost beyond our capabilities of measurement. Rate of recovery for these exposure energies was nearly identical to that of the more intense exposure even though these less intense exposures were presented for nearly 10 min longer. For the least intense beam (0.1 uW) the rate of the shift in acuity was similar to that observed with the 1 uW beam but the maximum deficit was significantly less (80% of pre-exposure level as opposed to >90% of this level). Again when the beam was turned off, the animal's acuity returned to its pre-exposure level in approximately 10 min. The position of the "cloud" covered the gap in the discriminanda which made visual resolution of it difficult regardless of the retinal area employed.

In the next series of figures the position of the laser "cloud" was positioned further off-axis (2^{o}) to facilitate the animal's ability to track



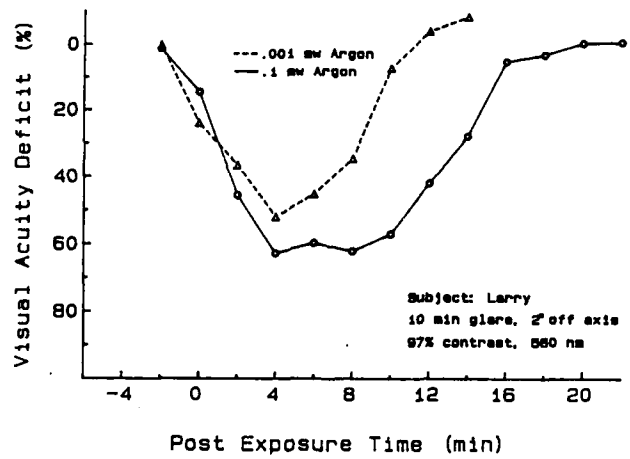


Figure 8. Shifts in achromatic visual acuity in two animals during and immediately following two different low-intensity, 10 min Argon exposures - glare effects. This animal was exposed to a 200 micron spot of either 0.1 or 0.001 uW for approximately 10 minutes from an Argon laser. During this time the animal's acuity was tracked using the up and down procedure. The position of the beam relative to the break in the Landolt ring was 2.0^{0} from its center but still covered the animal's view of it. The termination point for each exposure is indicated by an arrow (marked "off") while its onset was at the "0" mark on the abscissa. The data points represent the mean of each running two minutes of acuity testing. Visual acuity was tested either using low contrast (40%), achromatic backgrounds (upper graph) or chromatic (560 nm), high contrast (97%) backgrounds.

his visual acuity in the presence of the laser irradiation. In Figure 8A and 9, "clouds" of two different energy levels are shown for discriminanda

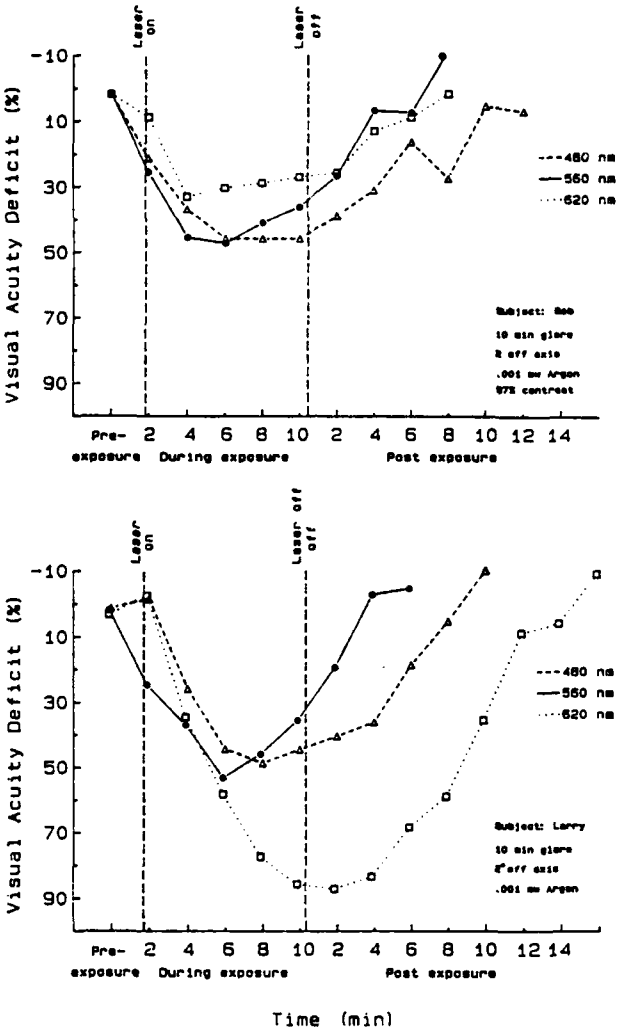


Figure 9. Shifts in visual acuity measured with different chromatic backgrounds during and immediately following low-intensity, 10 min Argon exposures - glare effects. Acuity was tested prior to, during, and immediately following low-intensity (0.001 mW) Argon exposures. The exposure lasted 10 min and was centered 2° off axis although still covering the gap in the Landolt rings. The onset and termination points of laser irradiation are shown by the dotted lines through each figure. The upper graphs represent the mean running acuity of one animal (Bob) and the bottom graphs the acuity of a second animal (Larry) exposed and tested under similar conditions. The different monochromatic test backgrounds were equated for equal numbers of quanta and were presented under maximum photopic conditions. Acuity was tracked using the up and down procedure during the entire course of laser irradiation.

presented against low-contrast achromatic (Figure 8A) backgrounds and against high-contrast chromatic (Figure 8B) backgrounds. The duration of the exposures for each were identical and lasted for a 10 min period during the animal's test session. Two different animals are presented in this figure. For visual targets on achromatic backgrounds, opening the laser shutter elicited either a 40% (0.001 mW) drop or 70% drop (.1 mW) depending upon the energy level employed. In the case of the more intense "cloud" the acuity level remained depressed for the full duration of the exposure while with the lesser energy "cloud" the animal's acuity began to recover prior to the termination of the exposure. When chromatic backgrounds of intermediate spectral distribution (560 nm) were employed, the drop in acuity was somewhat greater for the lower energy "cloud" but similar for the higher energy "cloud". Positioning the beam slightly off-axis did reduce the size of the initial deficit but was still disruptive despite it more peripheral location relative to the animal's fixation point and the critical figure of the Landolt ring.

In the next figure (Figure 9) the visual acuities of two animals are shown during and immediately following exposure to a 10 min, 0.001 mW Argon field that was again 2^0 off-axis. Both animals were exposed to a similar laser "cloud" and were tested using three different chromatic (480, 560, and 620 nm) backgrounds. For one subject (upper curves) the 514.5 laser "cloud" produced the maximum effect when the animal was required to make the discrimination against a 620 nm background. In this case, acuity decreased to approximately 85% of its pre-exposure rate during the time the laser "cloud" was presented. Acuity returned to its baseline level approximately 16 min after the termination of the irradiation. For targets against 560 and 480 nm backgrounds, on the other hand, the acuity deficit was reduced to 50% of its pre-exposure level during irradiation and the recovery in visual acuity began

before the laser field was terminated. Full recovery occurred 12 minutes after exposure for targets on 480 nm backgrounds and within 6 minutes for

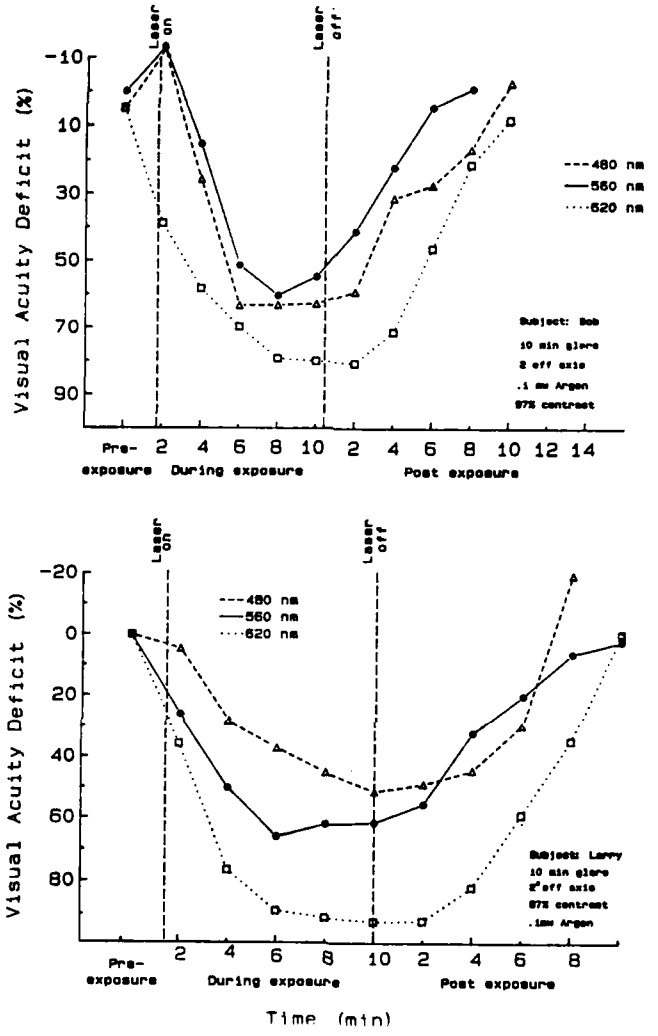


Figure 10. Shifts in visual acuity measured with different chromatic backgrounds during and immediately following low-intensity, 10 min Argon exposures - glare effects. Acuity was tested prior to, during, and immediately following low-intensity (0.1 mW) Argon exposures. The exposure lasted 10 min and was centered 2^0 off axis although still covering the gap in the Landolt rings. This exposure level was approximately 100 times that shown elsewhere. The onset and termination points of laser irradiation are shown by the dotted lines through each figure. The upper graphs represent the mean running acuity of one animal (Bob) and the bottom graphs the acuity of a second animal (Larry) exposed and tested under similar conditions. The different monochromatic test backgrounds were equated for equal numbers of quanta and were presented under maximum photopic conditions. Acuity was tracked using the up and down procedure during the entire course of laser irradiation.

targets on 560 nm backgrounds. A second animal (lower curves) tested under similar viewing conditions showed similar initial and recovery decrements for 480 and 560 nm backgrounds but, unlike the previous animal, this animal demonstrated the least decline in acuity and the fastest recovery when 620 nm backgrounds were used to measure visual acuity.

In Figure 10 the two same animals were exposed to a laser "cloud" that was 100 times greater in energy than that shown in Figure 10. This energy density, while intense, was still calculated to be significantly below that necessary to produce any permanent functional changes for this type of exposure condition. The chromatic (480, 560, 620 nm) and contrast (high) conditions under which the visual deficits were computed were identical to that used in Figure 9. The elicited acuity deficits for both animals in this case were more consistent with each other and both animals demonstrated a significant drop in acuity when 620 nm backgrounds were used to measure visual acuity. The drop was between 80 - 90% of the animals' pre-exposure levels and this deficit was maintained for the duration of the laser exposure. Immediately following the termination of the laser exposure, both animals began a gradual recovery in visual acuity which took approximately 10 min. For both 480 and 560 nm backgrounds, the drop in acuity was reduced (50 - 60% of pre-exposure levels) and recovery following the termination of the exposure was generally more rapid.

The same two animals were again tested using the same two energy levels for achromatic backgrounds which differed in contrast between the light field and darkened discriminanda. Figure 11 shows the deficit during and immediately following the lower level laser exposure (0.001 mW) when tested with 40%, 60% and 97% contrast targets. For one animal (upper graph), the lowest and highest contrast targets (40% and 97%) produced the greatest observed deficit during exposure (90%) although this animal appeared to

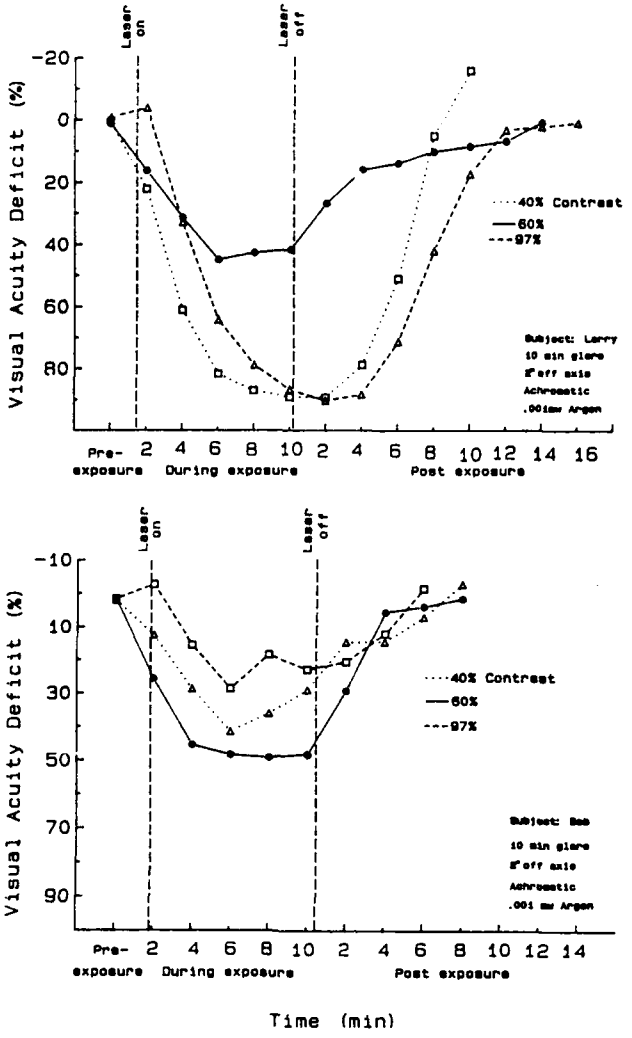


Figure 11. Shifts in visual acuity measured with different contrast backgrounds during and following low-intensity, 10 min Argon exposures - glare effects. Acuity was tested prior to, during, and immediately following low-intensity (0.001 mW) Argon exposures. The exposure lasted 10 min and was centered 2° off axis although still covering the gap in the Landolt rings. This exposure level is the same as that presented in Figure 9. The onset and termination points of laser irradiation are shown by the dotted lines through each figure. The upper graphs represent the mean running acuity of one animal (Larry) and the bottom graphs the acuity of a second animal (Bob) exposed and tested under similar conditions. The different contrast targets were produced by flooding the viewing screen with a second, diffusing light source besides that produced by the image projector. All backgrounds were equated for equal overall luminances. Acuity was tracked using the up and down procedure during the entire course of laser irradiation.

recover more quickly to the lower (40%) contrast target when the laser exposure was terminated. In both cases the animal had fully recovered from

the exposure within 14 min of its termination. For the second animal (lower graphs), the observed deficit was least when derived using the highest

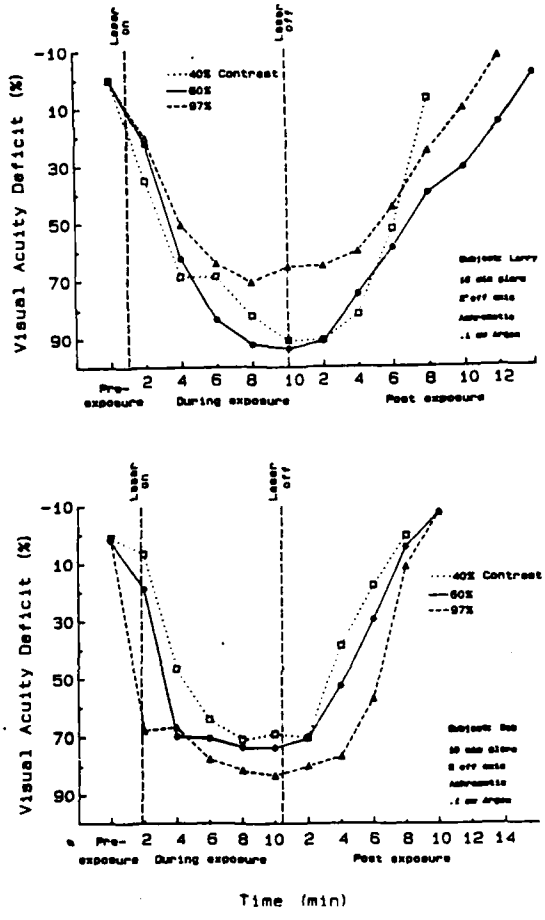


Figure 12. Shifts in visual acuity measured with different contrast backgrounds during and immediately following low-intensity, 10 min Argon exposures - glare effects. . The 0.1 mW exposure was 100 times the energy of that presented in Figure 9 and lasted 10 min. It was centered 2° off axis although it still partially covered the gaps in the Landolt rings. This exposure level is the same as that presented in Figure 8. The onset and termination points of laser irradiation are shown by the dotted lines through each figure. The upper graphs represent the mean running acuity of one animal (Larry) and the bottom graphs the acuity of a second animal (Bob) exposed and tested under similar conditions. The different contrast targets were produced by flooding the viewing screen with a second, diffusing light source besides that produced by the image projector. All backgrounds were equated for equal overall luminances. Acuity was tracked using the up and down procedure during the entire course of laser irradiation.

contrast targets (20%) and most when using the intermediate contrast targets (50%). Overall, however, the deficits elicited and recoveries following laser termination in this second animal did not vary significantly across viewing conditions. This animal demonstrated a similar phenomenon when tested with different chromatic backgrounds at this energy level.

These same two animals (see Figure 12) were again tested using a laser exposure level 100 times that shown in Figure 11. As was the case in Figure 10, the animal's visual acuity was tested using several different contrast targets (40, 60, and 97%). With this higher energy laser exposure, the animal's visual acuity for each of the different viewing conditions decreased markedly to 70-90% of its pre-exposure level and remained depressed during the full 10 min laser exposure. Recovery in all cases occurred within 8 to 12 minutes after the laser exposure was terminated.

DISCUSSION

The initial effect of a brief laser exposure focused on the fovea was to produce an immediate shift in visual sensitivity followed by a gradual recovery in sensitivity over time. In a previous report, we described a method for producing retinal exposures from a laser source in an awake, task-oriented subject. This method was used during the current effort and allowed for the measurement of rhesus visual acuity immediately following laser exposure thereby allowing for the exploration of transient and permanent function deficits for exposure energies at and below the ED_{50}.

Our results demonstrate that exposure of the fovea to a brief, isolated flash of coherent light produces an immediate, but dependent upon the energy of the exposure, often transient change in visual functioning. The magnitude

of the deficit was related to the size of the retinal exposure while the duration time for full recovery, when possible, was a function of laser energy somewhat independent of spot size. Once exposed, our animals maintained vigil and continued to respond to Landolt rings provided the gap sizes were significantly larger in visual angle to accommodate the animal's decreased foveal vision. Our data suggest that our animals did not change their criterion for detection (beta value) of the critical feature in the Landolt ring, as indicated by their unchanged false alarm rate for targets below their new threshold level. What did change was the animal's sensitivity (d') to resolve this spatial task. The fact that laser exposures did not result in a total functional impairment implies that the animals quickly learned to employ alternative, unexposed retinal areas to make the required discrimination. Given the size of our exposing beam, these areas would normally be outside the foveal region, in areas where spatial resolution is reduced. The magnitude of the initial deficit and its dependence on beam diameter supports this parafoveal hypothesis. An alternative hypothesis, however, might be that laser exposure resulted in an incomplete saturation of the photoreceptors and the resultant acuity levels obtained represented the activity of nondepleted foveal photoreceptors. Recovery would then represent the time required for affected foveal photoreceptors to again become fully functional. If this hypothesis was correct, however, one would expect that both the magnitude and the duration of any elicited deficit in visual acuity would be dependent upon exposure energy. Our results clearly indicate that only recovery time was related to exposure energy suggesting that the former, parafoveal hypothesis, more accurately accounts for our observed visual deficits.

The relatively large deficits (50% to 90%) produced by even our minimal diameter beams (50 micron spot on the retina) could be explained in terms of the influences of involuntary eye movements. Since our exposures typically

were 100 msec in duration, the actual diameter of the laser spot on the retina was somewhat larger than indicated here since the animal's eye was in constant motion during the 100 msec flash. The relatively short duration of this flash did prevent the animal from voluntarily moving his eye away from the bright light source but the rapid, irregular involuntary eye movements naturally occurring during any fixation would have smeared the image across a larger than initially predicted area. This might explain why even relatively small diameter retinal exposures (50 microns) produced a somewhat larger and longer decrement in postexposure visual acuity than might otherwise be expected. Given the size of the central fovea and the small diameter of our minimal spot, one might expect not to observe any shift in postexposure acuity with this type of irradiation since the animal should still be able to use unexposed regions of the fovea to make the required visual discrimination. Reducing the duration of the exposure below 100 msec might therefore produce no significant deficit in postexposure acuity especially when relatively small diameter spots are employed. Increasing the exposure duration above 100 msec, on the other hand, might be expected to have no greater effect over those previously observed since, for these longer durations, the animal's voluntary gaze away from the spot would reduce its foveal consequences. In our studies, very short duration exposures (<50 msec) produce little or no observed temporary deficits in visual acuity for those energy levels that were below the ED_{50} level. In subsequent studies we have explored the effects that very intense (densities significantly above the ED_{50}) exposures have on postexposure acuity when minimal diameter (<50 microns) spots are employed. This type of exposure typically produces no significant drop in baseline acuity although the animal's performance in the exposed eye becomes much more erratic. Multiple exposures of this nature eventually do produce a consistent long term drop in postexposure acuity as the lesion site increasingly spreads

across the fovea.

Our glare experiments suggest that even relatively low-level laser irradiation can have significant effects on the resolution of a visual target when viewed through the laser "cloud." The drop in visual sensitivity during exposure was greater than observed for the brief exposure condition although recovery was more rapid once the laser "cloud" was removed. During the 10 min exposure, often acuity remained depressed without any sign of recovery. When the "cloud" was positioned slightly off-axis, the decrement in visual acuity was somewhat reduced although performance under these conditions was still significantly depressed when compared to the pre-exposure condition. Exposing our animals repeatedly to these low-level, relatively long duration exposures produced no permanent shift in visual sensitivity and recovery was always complete within 15 - 20 min of its termination. These results do suggest, however, that even laser exposures of relatively low energy can produce significant disruptions of visual behavior that may last for some time following the termination of the exposure.

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